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SCHNIZER, RICHARD A	

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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,398	JOHN, CONSTANCE MARY	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *2,4-6,19 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3,7-18,22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/10/03. Applicants election with traverse of group 2 and the species of neurotrophins is acknowledged. Traversal is on the grounds that it would be inefficient to search and examine the different inventions separately, while admitting that they are classified differently. This is unpersuasive because Applicant as failed to show that the inventions are not separate or distinct or classified differently, and has presented no evidence that a complete search and examination of all the inventions would unduly burden the Examiner. Applicant is reminded that should the linking claim(s) be found allowable, the restricted inventions will be rejoined. In this Action, the linking claims will be examined to the extent necessary to determine if they are allowable.

It is noted that Applicant wished to "conditionally withdraw" claims 1, 2, and 4-24 pending reconsideration of the restriction requirement. The Examiner is unaware of any mechanism by which Applicant can withdraw claims other than by cancellation. In the Examiner's opinion, Applicant did not wish to cancel these claims, so they remain pending. Clarification of Applicant's wishes in this regard is requested.

Claims 1-24 are pending in the Application. Claims 1, 3, 7-18, 20-22 and 24 are generic to the elected invention. Claims 2, 4-6, 19, and 23 are withdrawn from consideration as drawn to a non-elected invention. Applicant timely traversed the restriction requirement. Claims 1 and 12 are independent linking claims from which linking claims 7-11 and 13-24 depend, respectively. Accordingly, claims 1 and 12 were examined to the extent necessary to determine patentability, in order to determine

whether or not the restricted inventions should be rejoined. Claim 3 will be examined completely. As seen below, claims 1 and 12 are unpatentable due to rejection under 35 USC sections 102 and 112, thus their dependents are not patentable and no linking claims are rejoined. As a courtesy to Applicant, all elected claims have been examined for compliance with 35 USC 112, second paragraph, and the rejections under 35 USC 112, first paragraph and 35 USC 102 list all claims that lack enablement or are anticipated by the cited art, respectively.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It was not executed in accordance with either 37 CFR 1.66 or 1.68. The oath is unsigned.

Specification

The specification is objected to because it is 128 pages but lacks pages numbered 94-99, while containing pages numbered 100-134. In previous years, the Examiner or the Legal Instruments Examiner would correct this problem and cite 37 CFR 1.121. However this application is in the form of an electronic image file, and the PTO has no mechanism for correcting such errors in electronic image files. Applicant should file an amendment to the specification correcting the error.

The specification is also objected to because it contains nonsensical text characters such as boxes. See e.g., page 7, lines 4, 6, 13, 15, and 16.

Claim Objections

Claim 12 is objected to because it is ungrammatical. Insertion of the word "have" immediately before the phrase "been isolated" is suggested.

Claim Interpretation

Claims 1, 3, and 7-11 are drawn to methods of providing a biologically active moiety by administering cells that are naturally immune privileged and that have been isolated and genetically modified in a laboratory apparatus so as to express said biologically active moiety in pharmacologically effective amounts in vivo. Claims 12-18, 20-22, and 24 are drawn to compositions comprising cells that are naturally immune privileged and that have been isolated and genetically modified in a laboratory apparatus so as to express a biologically active moiety in pharmacologically effective amounts in vivo.

The term "biologically active moiety" is not defined by the specification in a limiting manner, but at page 20, line 25 it teaches that the term includes polypeptides or the product of a polypeptide such as a neurotransmitter. As such, the term "biological moiety" is interpreted to include all gene products and all biomolecules that are produced by gene products, e.g. products of enzyme catalysis and polypeptide metabolism.

The specification provides a detailed discussion of immune privilege at pages 1-10. The term "immune privileged" is a term of art that refers generally to sites and tissues where grafts of foreign tissue survive for extended periods relative to sites that are not privileged. Further, grafts of immune privileged tissues are more resistant to immune rejection than are grafts of non-privileged tissues. The characteristics of cells that contribute to immune privilege are not completely understood, and immune privilege is a complex property mediated by multiple molecules in an unpredictable fashion. The specification teaches that different types of immune-privileged cells are biologically unique in the way that they create their immune-privilege status, such that the ability of different cells to survive allogeneic implantation will vary. The specification identifies several molecules that are involved in mediation of immune privilege, but it is apparent that due to inherent differences in various cells types, one cannot predict what set of molecules is required to make any one cell immune-privileged. As such, it is the inventors aim to use naturally occurring immune privileged cells as platforms for heterologous gene expression, rather than to modify cells to become immune privileged, or to coadminister immune privileged cells together with non-privileged cells that express a desired gene product.

The phrase "pharmacologically effective amount" is not defined in the specification. According to Steadman's Medical Dictionary (26th Edition, 1995) "pharmacology" as the science of drugs including materia medica, toxicology and therapeutics. In the same dictionary, "drug" is defined as a "therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or

cure of disease in man and animal." Thus, a "pharmacologically effective amount" is interpreted as an amount that allows the prevention, diagnosis, alleviation, treatment, or cure of a disease in an animal to which the substance is administered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Written Description

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 14 is specifically drawn to cells that naturally express a moiety in amounts that are not pharmacologically effective. However, the specification fails to provide adequate guidance for any specific pharmacological moiety as to what amount is pharmacologically effective, or what cells express a given moiety in a pharmacological vs. subpharmacological amount. The written description requirement can be satisfied for genus claims by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between

structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In this case the specification fails to identify a single cell that expresses a biological moiety, but only in subpharmacological amounts. The specification fails to describe what is, and is not, a subpharmacological amount of any biological moiety in any context. Because it is not conventional in the art to identify cells which express a given moiety, but do so only in subpharmacological amounts, some guidance or description in the specification is warranted. In the absence of such description, one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time of filing.

Scope of Enablement

Claims 1, 3, 7-18, 20-22, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and dependents are indefinite because metes and bounds of the claims are unclear. These claims are directed to methods of providing an active moiety, but it is unclear what are the method steps. It is clear that the methods require "administering cells". The claims then describe the type of cells to be administered. However, it is unclear whether or not the phrase "such that said cells express said biologically active moiety in pharmacologically effective amounts in vivo" is a method step, or if it is a description of the capability of the type of cell to be administered. It is not clear that the claims contain the essential method step of describing where, or to what, the cells

should be administered. As a result it is unclear to what the biologically active moiety is provided.

Claim 7 is indefinite because the metes and bounds of the group of non-viral physical methods are unclear. Applicant sets forth a group of methods from which a method may be selected, but stipulates that the group is not limited to the recited members. One of skill in the art cannot know what other methods Applicant intends the group to contain.

Claim 8 is indefinite because the metes and bounds of the group of viral vectors is unclear. Applicant sets forth a group of vectors from which a vector may be selected, but stipulates that the group is not limited to the recited members. One of skill in the art cannot know what other vectors Applicant intends the group to contain.

Claim 12 and dependents are indefinite because they recite "said biologically active moiety" without antecedent basis. These claims also refer to "pharmacologically effect amounts". The use of the plural "amounts" renders these claims indefinite because, while it implies that each moiety is pharmacologically effective in more than one amount it is unclear what amounts is referred to

Claims 13 and 14 are indefinite because it is unclear what is intended by a moiety that is not "naturally expressed" by said cells. This phrase could be interpreted as meaning "is not expressed by natural means", or alternatively could mean that the moiety is not endogenous to the cell.

Claim 22 is indefinite because it is drawn to the "method" of claim 12, but claim 12 is drawn to a composition, not a method. Substitution of "composition" for "method" in claim 22 is suggested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7-18, 20-22, and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of providing a biologically active moiety in vivo by implanting in an individual Sertoli cells that have been isolated and modified in a laboratory apparatus so as to express said biologically active moiety in pharmacologically effective amounts in vivo does not reasonably provide enablement for such methods using any other type of naturally immune privileged cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention is drawn to methods of providing a biologically active moiety in vivo in pharmacologically active amounts by administering cells to an animal, wherein the cells are naturally immune privileged and have been genetically modified to produce the biologically active moiety. Claims are 12-18, 20-22,and 24, drawn to compositions with a required characteristic of expressing a biologically active moiety in

vivo in pharmacologically active amounts. The elected biologically active moiety is a neurotrophin.

State of the prior art

The prior art taught that Sertoli cells could be transplanted to provide immunologically privileged sites to support cells intended to treat disorders such as diabetes. For example, Selawry et al (US Patent 5,725,854, issued 3/10/98) taught a method of treating a disease that results from a deficiency of a biological factor in a mammal wherein said method comprises administering Sertoli cells and a therapeutically effective amount of cells that produce said biological factor to a mammal, wherein said Sertoli cells are administered in an amount effective to create an immunologically privileged site. See claim 1. The prior art also taught that unmodified Sertoli cells could be used to treat Parkinson's disease. For example Sanberg et al (US Patent 5702700) taught a method of generating in situ trophic factors for ameliorating behavioral deficits caused by Parkinson's Disease by transplanting Sertoli cells utilizing stereotaxic delivery into the brain of an adult mammal who suffers from Parkinson's Disease. See claim 1.

A variety of publications shows that cells can be genetically modified to secrete pharmacologically effective amounts of neurotrophins in vivo, and that damage to the CNS can be treated by implantation of such cells. See e.g. Arenas et al (Nature, (1994 Jan 27) 367 (6461) 368-71), Ebendal et al (Journal of Neurology, (1994 Dec) 242 (1 Suppl 1) S5-7), and Martinez-Serrano et al (Journal of Neuroscience (1996 Aug 1) 16 (15) 4604-16) who teach the use of genetically modified cells including fibroblasts,

immortalized skeletal muscle cells, and neural stem cells, respectively. Gage et al (US Patent 5,082,670) taught a method for treating defective, diseased or damaged cells in the mammalian central nervous system comprising grafting a donor cell from the same mammalian species into the central nervous system, said donor cells genetically modified to produce a functional molecule in a sufficient amount to ameliorate said defective, diseased or damaged cells in the central nervous system.

Also the prior art teaches methods of producing adenine deaminase by transducing T cells with a gene encoding adenine deaminase. See Culver et al (Proc. Nat. Acad. Sci. USA 88, 3155, 1991). Note that, in view of claim 5, T cells are considered to be immune privileged.

Guidance and working examples in the specification

The specification teaches no working example of any method of using genetically modified, naturally immune privileged cells to produce a pharmacologically effective amount of any biological moiety in any organism in vivo. The specification teaches a number of prophetic examples, and presents prior art data showing treatment of spinal cord injury by transplantation into the spinal cord of fibroblasts genetically modified to secrete neurotrophin 3 (NT-3) (see Fig. 9). The specification asserts that Sertoli cells transfected with an NT-3 expression vector and transplanted into the spinal cord express NT-3. The data is presented as photomicrographs in Fig. 15, but the photomicrographs furnished to the PTO are of insufficient quality to allow evaluation of any data. The specification teaches that culture supernatants of transfected Sertoli cells contained sufficient NT-3 to cause neurite outgrowth in an in vitro assay, however,

the significance of the data is unclear (see Fig. 15). The sample size was very low, only 3 samples per condition, only two conditions were tested (1ml supernatant and 2 ml supernatant), and the experiment in which 2 ml of supernatant was used appeared to give insignificant results.

Although the instant claims require that administered cells must be immune privileged, the specification makes clear that the nature of immune privilege is poorly understood and unpredictable. The specification identifies several molecules that are involved in mediation of immune privilege, but it is apparent that due to inherent differences in various cells types, one cannot predict what is the minimum set of molecules required to make any one cell type immune-privileged. Also, the effect on immune privilege of genetic modification of cells is unpredictable. Although the specification teaches that certain genetically modified cells continue to express Fas ligand, it is also clear that expression of Fas ligand is not necessarily sufficient to ensure immune privilege. See e.g. paragraph bridging pages 8 and 9. Furthermore, in view of the paragraph bridging pages 8 and 9 of the specification, it appears that immune privilege is not so much a property of specific cells as it is a property of specific tissues or body cavities. For example, the specification teaches that a particular Fas-L-expressing tissue transplanted into a host was immune privileged only in the presence of extracellular TGF-beta. Accordingly, it appears that, at least in some situations, cells depend upon extracellular factors for immune privilege such that a cell that is immune privileged in one in vivo location may not be immune privileged in another location that lacks the appropriate extracellular milieu. The specification clearly envisions

transplanting cells to locations other than those from which they originate, but fails to provide adequate guidance as to which cells require exogenous factors for immune privilege, what those factors are, and what in vivo locations will provide them for a given cell type. As a result it is unpredictable as to whether or not genetically modified cells, such as for example placental or Paneth cells, particularly those that have undergone genetic changes rendering them immortalized (see e.g. claim 18), will retain their naturally immune privileged status.

Claim 14 is specifically drawn to cells that naturally express a moiety in amounts that are not pharmacologically effective. However, the specification fails to provide adequate guidance for any specific pharmacological moiety as to what amount is pharmacologically effective, or what cells express a given moiety in a pharmacological vs. subpharmacological amount. Absent such guidance, one of skill in the art is left to make such determinations empirically. In view of the essentially unlimited number of moieties and pharmacological situations embraced by the claims, such experimentation in the absence of adequate guidance from the specification is undue.

In view of the unpredictable nature of immune privilege, particularly in respect to which cells require extracellular factors for immune privilege, and the failure to identify those factors or tissues that provide them, one of skill in the art would have to perform undue experimentation in order to practice the claimed invention with naturally immune privileged cells, other than Sertoli cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8, 9, 11-13, 15, and 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Culver et al (Proc. Nat. Acad. Sci. USA 88, 3155, 1991), as evidence by Roitt et al (In *Immunology*, Second Edition, J.B. Lippincott, 1989).

Culver teaches a method of genetically modifying mouse T lymphocytes with a retroviral expression construct encoding human adenosine deaminase (hADA). The T lymphocytes were infused into mice, and hADA was detected in spleen lysates of the animals. Absent evidence to the contrary the amount of ADA produced was sufficient to be pharmacologically effective. Note that the instant specification and claims state that T lymphocytes are immune-privileged cells. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430,

433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Because the method of Culver uses products and method steps identical to those claimed, Culver anticipates the claims.

Claim 11 is included in this rejection because Culver administers the cells into the circulatory system of the animal. As such one of skill in the art would expect the cells to circulate normally. Roitt et al teach that lymphocyte circulation includes the central nervous system. See pages 3.8-3.10 and Fig. 3.25 on page 3.9. Absent evidence to the contrary, the cells of Culver enter the central nervous system and claim 11 is anticipated.

Claim 21 is included in this rejection because it is a product by process claim in which the claimed product, although isolated from a transgenic animal, is indistinguishable from that taught by Culver.

Claims 1, 3, 7, 12, 13, 15, 18, 20-22 and 24.are rejected under 35 U.S.C. 102(b) as being anticipated by Builder et al (US Patent 5,451,660, issued 9/19/95).

Builder teaches methods of genetically modifying Sertoli cells to express neurotrophins. See column 7, lines 49 and 50; column 8, lines 7-10; column 9, lines 63-66; and column 12, lines 37, 43, and 54-59. Claims 1, 3, and 7 are included in this rejection based on an interpretation of these claims in which the phrase "such that said cells express said biologically active moiety in pharmacologically effective amounts in vivo" is not considered a method step. The recited "administering step" would be anticipated by the administration of cells to a culture flask during the processes of

selection and amplification as disclosed at column 12, lines 54-59. This rejection can be overcome by making clear that the claimed method requires administration of the cells to a recipient in vivo.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

Richard Schnizer, Ph.D.